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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,919	12/10/2003	David J. Yang	UTSC:841US	7351

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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	PAPER NUMBER
1618	
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10/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/732,919	YANG ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,14-17,23-28,31-51 and 60* is/are pending in the application.

4a) Of the above claim(s) *5,14-17,23-28 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,31-33,35-51 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/30/08 has been entered.

Acknowledgement of Receipt

Applicant's Response, filed 4/30/08, in reply to the Office Action mailed 11/5/07, is acknowledged and has been entered. Claims 1, 2, 5, 10 – 28, 31 – 51 and 60 are pending, of which claims 5, 10 – 28 and 34 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1, 2, 5, and 60 have been amended. Claims 3, 4, 6 – 13, 18 – 22, 29, 30 and 52 – 59 are cancelled. Claims 1, 2, 31 – 33, 35 – 51 and 60 are readable upon the elected invention and are examined herein on the merits for patentability.

Inventorship

In view of the papers filed 4/30/08, the inventorship in this nonprovisional application has been changed by the deletion of Jerry L. Bryant.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Response to Arguments

Applicant's arguments, see pages 12-13 of the Response, with respect to the obviousness-type double patenting rejections over the claims of US 6,692,724 and 7,067,111 have been fully considered, but they are not found to be persuasive for reasons set forth hereinbelow.

Applicant's arguments, see page 13 of the Response, with respect to the provisional obviousness-type double patenting rejections over the claims of copending application No. 10/672,763 and 11/405,334 have been fully considered, but they are not found to be persuasive for reasons set forth hereinbelow.

Applicant's arguments, see page 13 of the Response, with respect to the rejection of claim 60 under 35 U.S.C. 112, second paragraph, have been fully considered. The rejection has been WITHDRAWN as being overcome by amendment.

Applicant's arguments, see pages 14-17 of the Response, with respect to the rejection of claims 1, 2, 31-33, 35-51 and 60 under 35 U.S.C. 103(a) as being unpatentable over Iyer (J. Nucl. Med., 2001, 42, p. 96-104) in view of WO 01/91807

have been fully considered, and have been found to be persuasive in view of the declaration of David J. Yang, Dong Fang Yu, Chun-Wei Liu and E. Edmund Kim. The declaration is sufficient to overcome the WO 01/91807 reference as prior art. Therefore, the rejection has been WITHDRAWN.

Double Patenting

Claims 1,2 and 31-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of U.S. Patent No. 6,692,724. Claims 35-41 are rejected on the ground of nonstatutory obviousness-type double patenting over the claims of U.S. Patent No. 7,067,111 for reasons set forth in the previous Office Action.

Applicant argues on pages 12-13 of the Response that neither of the cited patents teach or suggest any of the targeting ligands of the claimed invention.

This is not found to be persuasive. It is well-known in the art to substitute one functionally equivalent targeting ligand for another, e.g. for site specific imaging of tumor, etc. As such it would have been obvious to one of ordinary skill to make such a substitution, and the claims are overlapping in scope.

Claim 38 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/672,763. Claims 42-51 are provisionally rejected on the ground of nonstatutory

obviousness-type double patenting over the claims of copending Application No. 11/405,334 for reasons set forth in the previous Office Action.

Applicant argues on page 13 of the Response that none of the targeting ligands are overlapping in scope with those set forth in the '763 or '334 applications.

This is not found to be persuasive. It is well-known in the art to substitute one functionally equivalent targeting ligand for another, e.g. for site specific imaging of tumor, etc. As such it would have been obvious to one of ordinary skill to make such a substitution, and the claims are overlapping in scope.

New Grounds for Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following references drawn to non-elected species were found during the search for the elected species related to the targeting ligand. It should not be interpreted that a comprehensive search was performed for all non-elected species.

Claims 1, 32, 33, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Srinivasan (US 5,310,536).

Srinivasan discloses amide-thiolate ligands having improved metal chelate formation kinetics. Such compounds include N_2S_2 ligands as shown in claim 4, where X is a functional group for use in coupling the ligand to a biomolecule (claim 4). Suitable biomolecule includes human serum albumin (column 3, line 32). The ligands and biomolecule conjugates described above are useful in diagnostic and radiotherapy applications. The compounds may be labeled with any suitable radionuclide favorable for radiotherapy, such as ^{186}Re, ^{90}Y, or for diagnostic purposes, such as ^{99m}Tc, ^{111}In, and ^{62}Cu (column 3, lines 43+). Imaging of tumor is disclosed (Example 6).

Claims 1, 32, 33, 38, 39 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness *et al.* (WO 98/047541, whereby US 6,610,269 is relied upon as equivalent).

Klaveness discloses a composition of matter of formula (1): V-L-R, where V is a vector moiety having affinity for an angiogenesis-related endothelial cell receptor, L is a linker moiety of a bond and R is a detectable moiety (abstract). With regard to V, particularly preferred vectors include VEGF antagonists, bFGF antagonists, thrombospondin and thrombospondin fragments, CD36 and growth factors (e.g. VEGF, bFGF, etc) (column 23, lines 28 – 30). The reporter is a chelatable metal or polyatomic metal-containing ion (i.e. TcO), including ^{99m}Tc, ^{90}Y, etc. (column 38, lines 31+). Chelating groups include N_2S_2, ethylenethioethyleneiminoacetic acid, etc (column 40, lines 14-37). Imaging of various cancers is disclosed (e.g. breast, etc.), Table 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 31-33, 35-48, 51 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer *et al.* (*J. Nucl. Med.*, 2001, 42, p. 96-105) in view of Zareneyrizi *et al.* (*Anti-Cancer Drugs*, 1999, 10, p. 685-692).

Iyer discloses 8-[^{18}F]fluoropenciclovir (FPCV) for monitoring expression of herpes simplex virus 1 thymidine kinase (HSV1-kt) reporter gene in cell culture and in vivo (abstract). Penciclovir is used as a reporter probe for PET imaging (pages 95-96).

Iyer teaches ^{18}F labeling of penciclovir, rather than ^{99m}Tc labeling via an N_2S_2 chelator.

Zareneyirizi discloses synthesis of [^{99m}Tc]ethylenedicysteine-colchicine for evaluation of antinagiogenic effect. Colchicine, a potent antiangiogenic agent, is known

to inhibit microtubule polymerization and cell arrest at metaphase. ^{99m}Tc labeled EC-COL was prepared to assess tumor microvascular density. Tissue distribution and planar imaging studies were evaluated in breast-tumor bearing rats (abstract). An amino analogue of cholchicine (COL-NH_2) was synthesized for conjugation to L,L-ethylenedicysteine (page 686, left column). See also Figure 1. Radiosynthesis of [^{99m}Tc]ethylenedicysteine-colchicine was achieved by addition of ^{99m}Tc into kit containing EC-COL, Na_2PO_4, ascorbic acid, and NaEDTA (page 686, right column). Zareneyirizi teaches that due to favorable physical characteristics as well as extremely low price, ^{99m}Tc has been preferred to label radiopharmaceuticals. Several compounds have been labeled with ^{99m}Tc using nitrogen and sulfur chelates. Bis-aminoethanethiol tetradentate ligands are known to form very stable Tc(V)O complexes on the basis of efficient binding fo the oxotechnetium group to two thiolsulfur and two amine nitrogen atoms. ^{99m}Tc-L,L-ethylenedicysteine ([^{99m}Tc]EC) is successful example of N_2S_2 chelates. EC can be labeled with ^{99m}Tc easily and efficiently with high radiochemical purity and stability, and is excreted through the kidney by active tubular transport (page 685, right column).

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute an alternative PET imaging radionuclide, e.g. ^{99m}Tc, for ^{18}F in the methods of Iyer. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Zareneyirizi teaches that ^{99m}Tc labeling of radiopharmaceuticals is preferred because of favorable physical characteristics as well as extremely low price (page 685). One would have had a

reasonable expectation of success in providing ^{99m}Tc in an ethylenedicysteine carrier, as Zareneyirizi teaches that such complexes form stable chelates with oxotechnetium. Furthermore, one would have found it obvious to modify penciclovir via an amino group so as to conjugate to EC in a similar manner as colchicine was amino-modified for conjugation to EC, as in Zareneyirizi, Figure 1.

Furthermore, it is well-known in the diagnostic arts to substitute one known reporter probe, or targeting moiety, for another. As such, it would have been obvious to one of ordinary skill to substitute penciclovir-NH_2 for colchicine-NH_2 on the [^{99m}Tc]EC carrier disclosed by Zareneyrizi. Such a substitution would have yielded the expected result of PET imaging of in vivo HSVI-tk reporter gene expression via a targeted [^{99m}Tc]EC conjugate.

Claims 1, 2, 31-33, 35-51 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer *et al.* (*J. Nucl. Med.*, 2001, 42, p. 96-105) in view of Zareneyrizi *et al.* (*Anti-Cancer Drugs*, 1999, 10, p. 685-692), further in view of Belinka (5,609,847).

The rejection over Iyer in view of Zareneyrizi is maintained as above.

Zareneyrizi teaches EDTA, rather than gluconate or glucarate, as a chelator in the kit. However, gluconate and glucarate are well-known in the art to be functionally equivalent chelators to EDTA, as shown by Belinka.

Belinka discloses pharmaceutical kits can be prepared comprising a carrier, stabilizer, or preservative. A preferred kit would further comprise a predetermined amount of a reducing agent and a stabilizer that includes a transchelator. A

transchelator as used herein denotes a chelating agent that is "weaker" than the constructs of the present invention. Thus, the transchelator stabilizes the reduced species of pertechnetate while allowing the construct to form a stable complex with the reduced metal. Suitable transchelators may be alkylenepolyaminocarboxylic acid compounds, such ethylenediaminetetraacetic acid (EDTA), hydroxyethylenediaminetriacetic acid (HEDTA), sodium glucoheptonate, sodium tartrate, sodium gluconate, etc. Depending on the nature of the metal eventually chosen, the kit can be used to prepare a radiodiagnostic agent or a radiotherapeutic agent (see column 19, lines 25-42).

It would have been obvious to one of ordinary skill in the art to substitute gluconate or glucarate for EDTA as functionally equivalent chelators in the kit disclosed by Zareneyirizi. Such a substitution would have resulted in the predictable outcome of providing a metal chelator in a kit for preparing a radionuclide.

Claim Objections

Claims 1, 2, 31 – 33, 35 – 51 and 60 are objected to because of the following informalities: in the Markush group of targeting ligands in claims 1 and 2, the following species are recited twice: herceptin, angiostatin, thalidomide. Appropriate correction is required.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS